REMARKS

Claims 22-25, 27-40, and 42 are pending. Claims 22-25 and 42 are currently under examination, and claims 27-40 have been withdrawn from consideration because of a restriction requirement. Claims 22-25 and 42 are rejected for obviousness over Guarna et al. (*J. Org. Chem.*, 1999, 64:7347-7364; hereafter "Guarna") or Cini et al. (*Eur. J. Org. Chem.* 2002, 873-880; hereafter "Cini").

Telephonic Interview

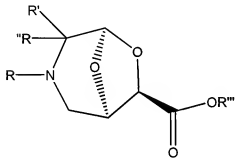
Applicants thank the SPE for the telephonic interview on December 30, 2008. In particular, the undersigned and the SPE discussed the fact that an amide precursor, as the term is used in Guarna, is the same as an intermediate, as the term is used in M.P.E.P. § 2144.09. The SPE was, however, concerned that certain compositions taught in Guarna and Cini could be considered to be pharmaceutical compositions. In reply to this concern raised in the telephonic interview, Applicants enclose a Declaration under 37 C.F.R. § 1.132 establishing that neither Guarna nor Cini teaches a pharmaceutical composition.

Rejections under 35 U.S.C. § 103

The obviousness rejection appears to be based on two grounds. The first is that, in the Office's view, it would be obvious to use certain compounds disclosed in Guarna and Cini in pharmaceutical compositions. The second is that, in the Office's view, Guarna and Cini teach pharmaceutical compositions as certain compounds are dissolved or suspended in water or ethanol in the references. Applicants traverse the rejections.

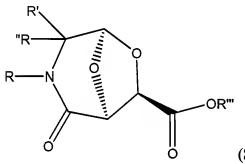
Nature of the Compounds of Guarna and Cini

Guarna and Cini describe the synthesis of dipeptide isoteres (or isoters), termed BTAas or BTSs, which may in turn be used to synthesize oligomers, as chiral auxiliaries, or as reverse turn inducers in peptide chains (Cini, page 873). BTAas have the general structure:



(Figure 1, Cini). BTSs have the structure of BTAas with R' as H, R" as $-CH_2OH$, and R''' as methyl (Figure 1, Cini).

As is taught in Guarna and Cini, dipeptide isoteres may be synthesized using amide precursors, termed BTAaOs in Guarna (page 7348). BTAaOs have the structure:



(Scheme 1, Guarna). The BTAaOs are in turned synthesized from simpler compounds, as shown in Scheme 1 of Guarna (page 7348). As is known in the art, an intermediate is "a chemical compound synthesized from simpler compounds and usually intended to be used in later syntheses of more complex products." (Merriam-Webster Dictionary, accessed June 11, 2009, copy attached). Accordingly, the BTAaOs disclosed in Guarna and Cini are intermediates as they are made from simpler compounds and used for the later synthesis of more complex products, e.g., modified peptides.

The teachings of Guarna and Cini on the synthesis of compounds can be summarized as follows:

Simpler compounds → BTAaOs → BTAas or BTSs → modified peptides

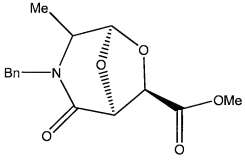
Importantly, the only pharmaceutical activity associated with any compounds discussed in Guarna and Cini is with respect to modified peptides that include a dipeptide isotere (Guarna, page 7347 and Cini, page 873). Neither the dipeptide isoteres nor the modified peptides of Guarna or Cini are encompassed by the present claims.

Given these teachings of Guarna and Cini, it is indisputable that the BTAaOs are intermediates, as the term is used in the art, and that the references provide no specific pharmaceutical utility for the BTAaOs themselves.

Claims 22-25

Claims 22-25 are directed to pharmaceutical compositions. These pharmaceutical compositions include a compound of formula I, as the active ingredient, and a pharmaceutically acceptable excipient. This invention is neither taught nor suggested by Guarna or Cini.

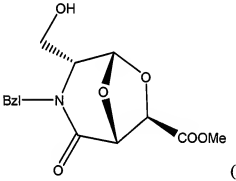
First, Applicants acknowledge that compound 12 disclosed in Guarna falls within the scope of formula I of claim 22. This compound has the structure:



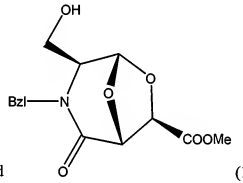
(Scheme 4, page 7353). Furthermore, this compound is a BTAaO compound, which as disclosed in Guarna is an intermediate in the synthesis of BTAas

and potentially modified peptides. Guarna at page 7353 specifically teaches: "Several reactions were carried out to test the stability of R-BTAa(O)-OMe derivatives or transform them into compounds suitable for peptide synthesis ... (Scheme 5)." As it clear from this statement of Guarna, compound 12, and other BTAaO compounds, are not suitable by themselves for peptide synthesis. That is, the only disclosed use of BTAaO compounds is for the synthesis of other compounds.

Similarly, Applicants acknowledge that compounds 16 and 20 disclosed in Cini fall within the scope of formula I of claim 22. These compounds have the structures:



(20) and



(16) (page 875).

Again these compounds are BTAaOs. Compound 16 is an intermediate in the synthesis of compound 14, as evidenced by Scheme 3 showing the continuation of the synthesis for three steps after the creation of compound 16. Compound 20 is a stereoisomer of compound 16, and the reference provides no explicit use for the compound in any context.

Response of the Office

In reply to these arguments, the Office has acknowledged that neither Guarna nor Cini teaches a pharmaceutical utility for the BTAaOs. For example, the Office states: "The reference [Guarna] teaches[es] the utility of BTAa(O) compounds as the *precursor* of dipeptide isosteres that can replace one or more amino acids in a bioactive peptide leading to modified structures

possibly displaying more favorable pharmacological properties." (Action, page 8; emphasis added).

The Office has maintained the rejection on the basis that the skilled artisan could formulate the BTAaOs in a pharmaceutically acceptable excipient. For example, the Office asserts, "a person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary." (Action, page 8). The only reason why one skilled in the art would formulate the BTAaOs in such an excipient provided by the Office is "the person of ordinary skill in the art would have been motivated to formulate the compounds of Cini et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Cini et al. teach that the compounds [are] precursors of compounds with pharmaceutical utility, and bioactive compounds are routinely formulated as pharmaceutical compositions..." (Action, page 8) Stated another way, the Office's position is that because drugs are formulated in pharmaceutically acceptable excipients, the skilled artisan would formulate any precursor compounds used in the synthesis of the drug in the same manner. This position is not supported by the cited references or established law.

Nonobviousness of Intermediates

As has been previously argued, M.P.E.P. § 2144.09 provides the appropriate legal standard for determining the patentability of active agents in view of intermediates. It states: "[I]f the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not ordinarily stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds

which have different uses." Thus, since the only disclosed use of the BTAaO compounds of Guarna and Cini is for the synthesis of other compounds, it is settled law that one skilled in the art would not investigate these intermediates with the expectation of employing them for any other use. Accordingly, in contrast to the Office's position, there is no reason why one skilled in the art would investigate BTAaO compounds disclosed in Guarna or Cini for pharmaceutical efficacy or formulate these compounds as pharmaceutical compositions because the only use disclosed for BTAaOs is in the synthesis of other compounds. The rejection should be reversed.

Pharmaceutically Acceptable Excipients and Diluents

In addition to the above, the Office also asserts that Cini teaches a pharmaceutical composition as compound 8 in the reference is dissolved in ethanol (page 878). As previously argued, solvents used in organic synthesis are not of pharmaceutically acceptable quality. That is, the solvents contain impurities or additives that make them unsuitable for human or veterinary use. Accordingly, the use of ethanol to dissolve compound 8 in Cini neither teaches nor suggests a pharmaceutical composition.

In reply to this argument, the Office states: "It would have been obvious to one of ordinary [skill] in the art to routinely formulate bioactive compounds in pharmaceutically acceptable excipients with quality or purity suitable for pharmaceutical use because Cini et al. teach that the compounds [are] precursors of compounds with pharmaceutical utility." (Action, page 9). While it or may not be obvious to formulate a *bioactive* compound in a pharmaceutically acceptable excipient or diluent, again there is no reason why one skilled in the art would formulate a *precursor*, i.e., a compound with no disclosed pharmaceutical utility, as if it were to be administered to a human or animal. Thus, the rejection should be withdrawn.

Applicants also note that the SPE expressed concern that ethanolic or aqueous solutions or suspensions of BTAaOs in Guarna or Cini were pharmaceutical compositions in the telephonic discussion of December 30, 2008. In reply, Applicants enclose a Declaration of Prof. Guarna, which explains that the solutions or suspensions of the two references are not pharmaceutical compositions.

As stated by Prof. Guarna, "[e]thanol or ethanolic solutions (as well as aqueous solutions) are cited in the two documents cited as prior art Guarna et al. 1999 and Cini et al. 2002 only as solvents used in the preparation of the compounds and therefore are not suitable for any pharmaceutical use either on humans or on animals." (Declaration, ¶ 6).

Prof. Guarna further comments on specific uses of ethanol and water in the references as follows.

With respect to compound 8 of Cini, Prof. Guarna notes that the ethanol employed to dissolve compound 8 for use in the synthesis of compound 16 (Scheme 3 and page 878) was not of pharmaceutically acceptable quality, leading to the conclusion that the solution of compound 8 in ethanol as employed in Cini is not a pharmaceutical composition. (Declaration, ¶ 7).

Prof. Guarna further notes that ethanol is cited with reference to the preparation of compound 21 in Cini (page 879). "In synthesizing compound 21, compound 18, that is belonging to the class of BTA(O) amide intermediates, is dissolved in THF (which is not a pharmaceutically acceptable solvent or diluent) and treated with a mixture of ethanol, sodium hydroxide and H_2O_2 which are reagents necessary to destroy the excess of the reagent $BH_3.Me_2S$." As declared by Prof. Guarna, this mixture of organic solvents and reagents is also not a pharmaceutically acceptable solvent or diluent for this compound. (Declaration, ¶ 7).

Prof. Guarna also states that the Guarna reference teaches that "the N-protected R-BTAa-(O)-OMe derivatives were easily transformed into the corresponding acids either under acid conditions with aqueous 2 N HCl or basic conditions with KOH/MeOH." With respect to specific compounds in the reference, Prof. Guarna states that compound 15 is prepared from compound 2 in a water suspension (page 7362), but "[t]he water employed to suspend compound 2 was not of pharmaceutically acceptable quality." Accordingly, the suspension of compound 2 in water in Guarna is also not a pharmaceutical composition (Declaration, ¶ 8).

In general, Prof. Guarna notes that the word "aqueous" appears only 6 times in Cini and in all the cases is in reference to salt solutions for the work-up treatment of reaction mixtures and not directly to dissolve the amide intermediates BTAaOs. Furthermore, the word "water" is present 13 times in Guarna and 8 times in Cini, but, except for compound 2 discussed above, it is only referred to as a solvent for salt solutions used for work-up of reaction mixtures, not for BTAaOs. For example, in preparation of intermediate compound 8 in Cini, "The organic phase (containing **8**) was washed with saturated aqueous $NaHCO_3$ and **water**, and dried with Na_2SO_4. After evaporation of the solvent (organic phase), the crude product was purified by chromatography (EtOAc/petroleum ether, 1:2, *Rf* 5 0.26), yielding **8**..." (page 877; emphasis added). Prof. Guarna thus concludes that "the prior art[, i.e., Guarna and Cini,] does not teach anything about the use of ethanol or water as pharmaceutically acceptable solvent or diluent." (Declaration, ¶ 9).

As discussed by Prof. Guarna, neither cited reference teaches or suggests the use of a pharmaceutically acceptable excipient or diluent in connection with a BTAaO compound, and this basis of the rejection should also be withdrawn.

Claim 42

With respect to claim 42, the compounds identified by the Office as disclosed in Guarna have been deleted, and this rejection may also be withdrawn. As this amendment presents claim 42 in better form for appeal, i.e., it renders the rejection moot, entry is warranted under 37 C.F.R. § 1.116 (b)(2).

CONCLUSION

Applicants submit that the amended claims are in condition for allowance, and this action is respectfully requested. Enclosed is a petition to extend the period for reply for three months, to and including June 11, 2009. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 6/11/09

J. Cooper McDonald, Ph.D.
Reg. No. 52,011

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

intermediate

6 entries found.

1 intermediate (adjective)
2 intermediate (noun)
3 intermediate (intransitive verb)

Main Entry: **2intermediate**
Function: *noun*
Date: 1650

1 : one that is intermediate
2 : MEDIATOR, GO-BETWEEN
3 a : a chemical compound synthesized from simpler compounds and usually intended to be used in later syntheses of more complex products **b :** a usually short-lived chemical species formed in a reaction as an intermediate step between the starting material and the final product
4 : an automobile larger than a compact but smaller than a full-sized automobile